REMARKS

Claims 1-16 are pending. Claims 13-16 have been added. Support for claims 13-14 can be found, for example, on page 24, lines 17-18 of the application. Support for claims 15-16 can be found, for example, on page 16, lines 20-21 of the application.

A. The Present Invention

Antiretroviral therapy regimens to combat infectious diseases--such as HAART therapy to slow the onset of AIDS--has appropriately been called a "lifetime sentence". Once the antiviral regimen is discontinued, virus levels in the blood begin to climb and the AIDS virus re-emerges. See BioWorld Today, "Even After Hyper Antiviral Pills, HIV Can Lurk in Body's Immune Cells to Pop Up Again One Day", Vol. 14, No. 140, col. 1, page 1, attached as Exhibit A. Given the serious long-term side-effects, high costs, and onerous dosing requirements placed on recipients of antiretroviral therapy, a method of potentiating immune response while freeing the patient from the "lifetime sentence" of antiretroviral therapy is desperately needed.

An embodiment of the present invention provides a method for the potentiation of an immune response to an infectious disease after the discontinuation of treatment for the infection. In accordance with the present invention, an HIV patient can discontinue antiretroviral therapy while keeping the infectious disease in remission. Immune response is enhanced by the administration of low doses of IL-2.

There is also a need to protect those individuals who, despite vaccination, develop the condition which the vaccination is designed to prevent. Applicants also provide a method for the

potentiation of an immune response prior to vaccination. Low dose IL-2 is administered prior to receiving a vaccination to protect that portion of the vaccinated population who would otherwise fail to mount an immune response to the vaccination.

There is likewise a need for more effective treatment of hepatitis C virus (HCV) without serious side-effects. Applicants provide a method for treatment of HCV by administering to a subject a composition comprising IL-2 in an amount effective to maintain immune enhancement without eliciting toxicity of Grade 1 or higher, as defined by the World Health Organization.

B. Rejection Under 35 U.S.C. § 103

Claims 1-12 stand been rejected as obvious over U.S. Patent No. 6,045,788 issued to Lane ("Lane"). Applicants respectfully submit that claims 1-12 and newly added dependent claims 13-16 are not obvious over Lane.

Although the Examiner admits that Lane does not teach the administration of IL-2 "in amounts sufficient to comply [with] the WHO grading system", the Examiner alleges that "one of ordinary skill in the art would have been motivated to follow such guidelines to ensure the safe administration of the compound." (Office Action dated July 2, 2003, paragraph 4). Applicants respectfully note that Lane calls for significantly higher dosing of IL-2:

> Although a dosage of 18 MU/day [million international units per day] is preferred, some patients may not be able to tolerate this high level of IL-2, and dosages of 6-12 MU/day may be used with benefit. (Lane, column 7, lines 44-47)

Even the lower dosage of 6-12 million international units per day is, in certain cases, *at least* 8-16 times the amount of IL-2 used in embodiments of the present invention (See application, page 10, line 24). The present invention provides for the administration IL-2 in amounts that would not result in the toxic side-effects caused by the teachings of Lane.

Independent claims 1 and 11 recite administering to a subject IL-2 in an amount without eliciting toxicity of Grade 1 or higher. As Lane teaches administration of IL-2 in amounts limited only by the ability of the patient to tolerate these toxic side-effects, Lane does not teach or suggest this limitation. Furthermore, one would not be motivated to administer IL-2 such that toxicity of Grade 1 or higher is avoided due to the high dosages called for in Lane. Accordingly, Applicants request that the obviousness rejection be withdrawn.

Furthermore, Lane does not teach the methods recited by the independent claims of the present invention. Independent claim 1 recites a method for the potentiation of an immune response to an infectious disease after the discontinuation of treatment for the infection or prior to vaccination comprising administering IL-2. Lane does not disclose administration of IL-2 after the discontinuation of treatment for an infectious disease or prior to vaccination. Claim 11 recites a method for treatment of hepatitis C virus. Lane does not disclose treatment of hepatitis C. Accordingly, these limitations are also not taught by Lane.

C. Conclusion

In sum, Lane teaches larger dosage amounts of IL-2, and Lane does not use these larger amounts of IL-2 in the recited methods of the present invention. In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Dated: October 2, 2003

Respectfully submitted,

By _____

Jason C. Chumney
Registration No.: 54,781
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 753-6237 (Fax)
Attorneys/Agents For Applicant

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Praecis Still Expects Plenaxis Approval Despite 3-Month Delay

By Aaron Lorenzo
Staff Writer

Praecis Pharmaceuticals Inc. continues to expect regulatory approval for Plenaxis despite an FDA decision to delay action on the new drug application by three months.

The agency recently informed the Waltham, Mass.-based company that instead of acting on the Plenaxis submission on Aug. 27, it would postpone the matter by 90 days. Praecis said the extension would allow the FDA to finalize its review of recently requested data, and also provide both parties time to finalize a risk-management program for Plenaxis.

"We're encouraged by our phone call as to the approvability of Plenaxis, and we expect it to be available to patients in the first quarter [of 2004]," Kevin McLaughlin, the company's chief financial officer, told *BioWorld Today*.

See Praecis, Page 2

Harlan Waksal Resigns; Focus At ImClone Squarely On Erbitux

By Kim Coghill
Washington Editor

WASHINGTON – The Waksal brothers era at imClone Systems Inc. is over, following the resignation of Harlan Waksal Monday as chief scientific officer and director.

"We hope ImClone is free of the negativity at this point in time, but how the stock will perform will hinge on both the near-term and long-term future of Erbitux," Cory Kasimov, an analyst with Ryan Beck & Co. in New York, told *BioWorld Today*. "Investors may perceive it as a positive, that neither of the Waksal brothers is with the company, but then again, it is the Waksal brothers who got Erbitux to the point it is today."

Harlan took over as CEO after his brother, Samuel, was arrested in June 2002 on a series of charges related to insider trading, securities fraud and bank fraud surround-

See ImClone, Page 4

Life-Threatening Hazard Of HAART?

Even After Hyper Antiviral Pills, HIV Can Lurk In Body's Immune Cells To Pop Up Again One Day

By David N. Leff
Science Editor

It's a HAART-less, cruel deception that the now-popular drug therapy against HIV, the AIDS virus, works so well that it may be life-threatening. Here's the paradoxical scenario: An HIV-infected patient, male or female, is prescribed a confusing quantity of antiretroviral pills aimed at reducing the virus from a perilous thrust toward AIDS down to a low, manageable blood level that keeps HIV safely on the reservation.

But it's asking a lot of the patient to remember when to take his medicine, in what order, and in relation to waking, eating and sleeping. Near-perfect compliance not only

See HIV, Page 7

ILEX Proposes Public Offering That Could Gross $115.9 Million

By Aaron Lorenzo
Staff Writer

ILEX Oncology Inc. reported plans to raise about $115.9 million through a public offering of 6 million common shares.

The San Antonio-based company plans to sell 5.5 million shares on its own, which would raise gross proceeds of $109.3 million based on Friday's $19.27 closing bid price of the stock. At the same time, the Cancer Therapy and Research Center Endowment, a current shareholder, plans to offer 500,000 shares to garner an additional $9.6 million. On Monday, ILEX's shares (NASDAQ:ILXO) dropped $1.06 to close at $18.36.

Both parties plan to grant a 30-day, 900,000-share overallotment option to the underwriters, a group that includes New York-based UBS Securities LLC as the offer-

See ILEX, Page 6

THOMSON

HIV

Continued from Page 1

wards off AIDS but abates the many severe symptoms of HIV infection. "Great!" the patient thinks. "It's working so well I can give up this regimen – at least for a few weeks or months."

HIV may be down but it's never out. Within a few weeks or months – sometimes years – experience shows, HIV has made a comeback. Symptoms have returned, virus in the blood has climbed alarmingly. The AIDS virus re-emerges when the HAART threat has gone away.

"Current opinion holds," suggests immunologist/virologist Simon Swingler at the University of Massachusetts in Worcester, "that HIV's infective particles enter and infect the immune system's CD4-positive cells. This is the first target reservoir the virus centers in its cross-hairs to disable the body's immune defenses."

Swingler is lead author of a report on this subject in *Nature* dated July 10, 2003. Its title: "HIV-1 Nef intersects the macrophage CD40-ligand signaling pathway to promote resting-cell infection." Its senior author is Mario Stevenson, UMass professor of molecular medicine.

"Probably, our finding suggests," Swingler observed, "that HIV latency is not necessarily dependent on where the virus is but on the activation state of the cell where its reservoir is located. A lot of people," he continued, "decided that it could be a physical compartment that is not accessible to drug therapy. HIV is involved so it can hide itself in plain sight."

How HIV Manipulates Immune System

"The mechanism it uses to do that," Swingler went on, "and how it manipulates the immune system, uses a pathway that nobody expected. Previously everybody understood that HIV replicated in actively cycling T lymphocytes. Whereas we show that the T cell only has to be in the very first phases of the cell cycle to become infected and produce viral proteins.

"And then once it's initiated into full activation it will produce complete particles, so it can hide itself from immune surveillance and yet be present. It's really the molecules involved in both the release from Nef-infected macrophages and how they affect antigens on macrophages. B cells, in turn, change the activation state for a fully or restricted productive replication.

"The prior dogma had two schools of thought," Swingler told *BioWorld Today*. "The HIV-infected T cell yet reverts to a complete latent state where there are no RNA transcripts from the viral genome and the proteins they made. Or they could infect a compartment, yet replicate at a low rate turnover so the particles are continuously reinfecting cells. We're showing that either of those soluble proteins can become fully activated at relatively high site of origin. They just sit in this viral reservoir, make these proteins and transcribe their RNA."

Does Swingler's finding then suggest that the antiretroviral therapy regimen, which is such a great hope now, must be a life sentence? Does the patient who is now staving off the HIV infection dare not to stop? "That is true," he commented. "Regardless of what we actually found in the cell cycle, that HAART effect has always been true. Our *Nature* paper really explains where else to look to target virally infected cells, and may suggest ways to get at the virus. Treating the patient with the antiretroviral load down to these set points. That's where it comes to two schools of thought. Now it comes down to three. Where you have a low turnover the virus cells, restricted by their cell-cycle position, are infected. And getting to those cells is the problem."

The crux of the HIV's virulence is a gene called "Nef."

Nef, Swingler explained, stands for "Negative Factor of viral replication. It was thought when the virus was isolated and grown in early tissue-culture days in the late '80s that if you removed the Nef gene, the virus replicated better. It was found out later that starting to use the virus in primary human cells and in animal models, progression to disease was very much a factor when Nef was present. If Nef was damaged or deleted," he went on, "you got a group of long-term nonprogressors, infected but tending not to progress to full-blown AIDS. The Nef genes, it's now understood, represent the more rapid pathogenic determinants of HIV infection in AIDS."

How To Eradicate Nef Gene?

Swingler points out that "most of the things to look at now would be figuring out how Nef orchestrates its signaling mechanism within a macrophage – and preventing it. That's certainly one area that we are trying to interfere with. We could try to move outside and work on neutralizing those soluble factors produced by macrophages. So the three cell types that we studied further were the macrophage, the B cell and the T cell, hopefully for any type of therapy.

"We found that infected macrophages expressed their release to chemokines. Nef induced release of chemokines sufficiently to allow these resting, latent cells to also become infected with HIV. These attracted purified T lymphocytes toward infected macrophages, expressed sufficiently to allow these resting latent T cells to also become infected with HIV. They had the same effect as expression of Nef, and were up-regulated from the same family of kinases, NF(κ)B. So the T cells cycled from G-zero to G-1 phase and become infectable by HIV. And the way for HIV to do that providing two molecules, soluble CD23 and ICAM, to affect the expression of the cognate ligands on B cells. Three or four of those ligands on B cells determined whether we got a resting T cell that fits into G1 and gets infectable.

"I'll be looking for viral proteins to form the targets for new HIV drugs," Swingler said. "We've already got the ones that get rid of the viral load to the very lowest blood level. But HAART therapy isn't going to stop death from HIV," he concluded, "unless we can target this new latency reservoir." ■